



⑪

Offenlegungsschrift 24 33 165

⑫

Aktenzeichen: P 24 33 165.5-42

⑬

Anmeldetag: 10. 7. 74

⑭

Offenlegungstag: 30. 1. 75

⑯

Unionspriorität:

⑰ ⑱ ⑲

13. 7. 73 Luxemburg 68016

⑳

Bezeichnung:

N-Acetylglycin-menthylester, Verfahren zu seiner Herstellung und Verwendung

㉑

Anmelder:

Unilever N.V., Rotterdam (Niederlande)

㉒

Vertreter:

Werth, A. van der, Dr.-Ing.; Lederer, E., Dipl.-Chem. Dr.; Pat.-Anw.
2000 Hamburg u. 8000 München

㉓

Erfinder:

Humbert, Francoise, Paris; Guth, Gerald, Franconville;
Tollard d'Audiffret, Yves, chemin de Stramousse par Cabris (Frankr.)

DT 24 33 165 A1

[19] Federal Republic of Germany, German Patent Office

A 23 6 1-226

A 61 K 7-22

Patent (Offenlegungsschrift)

[11] Publication No.: 24 33 165

[21] Application No.: P 24 33 165,5-42

[22] Application Date: 7/10/74

[43] Present Version Issued: 1/30/75

[30] (Union) Priority:

[31] File No.: 68016

[32] Date: 7/13/73

[33] Country: Luxembourg

[71] Applicant: Unilever N.V., Rotterdam (Netherlands)

[72] Inventors: Humbert, Françoise, Paris; Buth, Gerald, Franconville; Tollard d'Audiffret, Yves, chemin de Stramousse par Cabris (France)

[74] Representative: Werth, A. van der, Dr.-Ing.; Lederer, F., Dipl.-Chem. Dr.; Patent Attorneys, 2000 Hamburg and 8000 München

[54] Title: N-ACETYLGLYCINE MENTHYL ESTER, ITS MANUFACTURING PROCESS AND USE

The invention relates to N-acetylglycine menthyl ester, its manufacturing process and agents containing this ester.

Menthol produces a fresh or cool sensation through its action on the nerve endings in the oral and nasal region, and this refreshing effect is utilized by adding it to products for oral use. However, the use of menthol or products such as natural peppermint oils, which contain it, for this purpose is limited by the strength of the aroma and the burning sensation that

can be produced as a result.

Surprisingly, it has now been discovered that the menthyl ester of N-acetylglycine produces a long-lasting, cooling sensation and a refreshing effect with less dominant aroma and less burning sensation. Furthermore, the N-acetylglycine ester is far superior to other menthyl esters with very similar structures. Although some menthyl esters of amino acids therefore exhibit the refreshing effect, they generally have an ammonia odor, and their salts, such as the hydrochloride salt, have an unpleasant taste. Esters of menthyl with acetylated amino acids, which differ from glycine, exhibit the refreshing effect but are unacceptably bitter. The table on the next page lists the results of organoleptic studies conducted with some of these compounds for comparative purposes. For the investigations, 10 drops of a 10 percent alcohol solution of this compound were taken orally on a piece of sugar and the duration of the refreshing effect and the bitter action was measured. The invention therefore concerns the new compound in the form of the menthyl ester of N-acetylglycine, which can be used in compounds or agents for oral administration or ingestion.

In the process of the invention the menthyl ester of N-acetylglycine is produced by esterifying glycine with menthol and acetylating the glycine either before or after esterification. The esterification and acetylation can be performed by standard methods. Thus, menthol and glycine may be heated together in the presence of an acid catalyst, eg, sulfuric acid or p-toluenesulfonic acid, which are preferably used in excess over the amount needed for neutralizing the amino group of the glycine, the ester formed then being brought into contact with a base, eg, sodium carbonate, to release the

Table.

Compound	Refreshing effect	Duration (min)	Bitter effect	Duration (min)
Menthol	immediate and strong	15	strong	1.5
Menthyl ester of N-acetyl amino acids:				
Alanine	immediate and strong	16	very strong, then suddenly vanishing	5
α -Aminobutyric acid	immediate and moderate	17	moderately strong	5
Leucine	immediate and weak	5	weak to moderate	1
Glycine	weak at the beginning, takes 2 minutes to appear	20	weak, increases up to 1 min and then rapidly disappears	1

amino group. Subsequently the menthyl ester of glycine obtained is acetylated with an acetyl chloride or acetic anhydride. Preferably, however, the glycine is first acetylated and the N-acetylglycine then heated by heating [sic] with menthol in the presence of the acid catalyst, since this method affords a better product yield. The invention therefore relates both to a process in which the menthol ester of glycine is acetylated and to a process in which N-acetylglycine is esterified with menthol.

The inventive compositions or agents consist of the menthyl ester of N-acetylglycine and an orally acceptable excipient. By excipient we mean the rest of the agent or composition, regardless of whether some or all of it has

another function. The ester may be present in solution or suspension or may be adsorbed on the excipient or part of the excipient or encapsulated therein. Such compositions or agents may be present in solid form, eg, as powder or tablets, in paste form or liquid form, containing an effective ester quantity to produce the refreshing sensation after introduction into the mouth by releasing the ester from the composition or agent. Therefore, the ester is brought into contact with the surfaces of the oral cavity if a dental hygiene product or toothpaste containing it is used to brush the teeth; if a dentally effective lozenge containing it is sucked, if a chewing gum containing it is chewed and if a mouthwash containing it is used for washing the mouth. An effective amount of the ester is generally 0.025-2 weight percent; preferably 0.1-0.2 weight percent, relative to the composition, is used.

The composition or agent may contain a sweetening agent, eg, dextrose, levulose, saccharin, sodium cyclamate or a dihydrochalcone, and generally, from 0.01 to 5 weight percent of the sweetening agent is present, relative to the composition. The composition or agent usually contains a flavoring, eg, an aromatic oil, in the amount of 0.01-5 weight percent of the agent or composition.

Particularly relevant are dental hygiene agents in which the excipient contains a tooth polishing agent. Suitable tooth polishing agents are those commonly used in dental hygiene agents, eg, calcium carbonate, dicalcium orthophosphate, tricalcium orthophosphate, calcium pyrophosphate, insoluble sodium metaphosphate, hydrated aluminum oxide and hydrated diatomaceous earth and particles of thermally cured resin, such as urea-formaldehyde and melamine-formaldehyde resin. The amount of tooth polishing agent generally

ranges from 5 to 95.5 and preferably from 10 to 60 weight percent of the composition or agent as a function of the form of the dental hygiene agent. A tooth powder generally contains the polishing agent, a surfactant, a flavoring and a sweetener, while a toothpaste generally additionally contains water, a moisturizer, a binder and a preservative. Therefore, an inventive agent preferably contains a tooth polishing agent and a surfactant, eg, sodium lauryl sulfate, sodium coconut monoglyceride sulfanate, sodium N-lauroylsarcosinate, dioctyl sodium sulfosuccinate, sodium laurylsulfoacetate. Generally, 0.01-10 weight percent and preferably 0.5-5 weight percent of the surfactant is present, relative to the composition or agent.

Suitable as moisturizers are glycerin, propylene glycol, sorbitol and polyethylene glycols. Examples of suitable binders are starch, karaya resin, gum tragacanth, sodium alginate, extract of carrageenan, methylcellulose and carboxymethylcellulose sodium. Sodium benzoate and methyl-p-hydroxybenzoate are suitable preservatives. The amount of water, moisturizer and binder present depend on the consistency of the desired paste composition, but are generally such that the composition or agent can be pressed out of an aerosol container or a squeeze tube. A toothpaste may contain, for example, 10-30 weight percent water and 5-70 weight percent moisturizer. Usually from 0.1 to 10 weight percent and preferably from 0.2 to 5 weight percent binder is present, relative to the composition or agent.

Other constituents that can be added to a toothpaste are softeners, such as titanium dioxide, optical brighteners, bleaches, chloroform, urea, diammonium phosphate, film forming substances, eg, silicones, germicides, eg,

dichlorophen and hexachlorophen, chlorophyll derivatives, vitamins, antibiotics, enzymes, astringents and coloring agents.

The inventive compositions may also contain a cariostatic agent, eg, sodium fluoride, stannous fluoride or sodium monofluorophosphate. 0.01-1 weight percent and preferably 0.02-0.5 weight percent cariostatic agent, relative to the weight of the composition or agent, can be used. Other ingredients that can be used in a dental hygiene composition are given in Cosmetic Science and Technology by Balsam and Sagarin (Wiley-Interscience), 2nd edition (1972).

The pH produced in the mouth by the composition or agent should be within the range of 4-8 and preferably 4.5-6.5. To adjust to a suitable pH, citric acid may be used.

A suitable base for an excipient for a mouthwash composition can be provided by aqueous ethanol. Typical mouthwash ingredients suitable as excipients of mouthwash compositions are listed in the above-cited publication.

The compositions or agents of the invention may be produced from the ingredients by conventional methods in which the menthyl ester is added to the orally acceptable excipient, eg, to the excipients listed in the aforementioned publication.

The invention shall be described in the following on the basis of the following examples.

Example 1

A mixture of 23.4 g (0.2 mole) of N-acetylglycine obtained by acetylating glycine with acetic anhydride, 48 g of menthol, 5 g of p-toluenesulfonic acid,

280 mL of benzene and 120 mL of toluene was refluxed for 15 hr with removal of the water formed during esterification. The cooled solution was filtered and washed to neutrality with aqueous sodium bicarbonate solution and with water. The solvent was removed by evaporation, and the remaining oil was dissolved in 65 mL of hexane and cooled to 0°C. When the mixture was left to stand, 35.5 g of crystals of menthyl ester of N-acetylglycine precipitated. During recrystallization from hexane, an ester product was formed at F - 61-62°C.

Example 2

A mixture of 15 g (0.2 mole) glycine, 48 g menthol, 48 g p-toluenesulfonic acid, 280 mL benzene and 120 mL toluene was refluxed until esterification was complete. The solvent was evaporated and the residue extracted with ether, yielding the amino ester tosylate. The latter was hydrolyzed with sodium carbonate and the free amino ester isolated and purified by distillation under vacuum. 0.9 g amino ester, 8.5 mL acetic anhydride and 12.5 mL water were refluxed together for 10 min; the reaction product was cooled and the menthyl ester of N-acetylglycine recovered as in Example 1.

Example 3

A toothpaste was prepared by conventional methods from the following ingredients (in parts by weight):

Menthyl ester of N-acetylglycine	0.20
Diatomaceous earth	18
Sodium lauryl sulfate	1.5

Glycerin	58
Sodium saccharinate	0.15
Flavorings	
Bulgarian mint oil	0.32
Arvensis mint oil	0.34
Aqueous 1% thymol solution	0.02
Menthol	0.05
Natural anethole	0.04
Wintergreen oil	0.01
Clove oil	0.002
Vanilla tincture	0.017
Ceylon cinnamon oil	0.001
Water	21.35

When the teeth were brushed with this paste, a mintlike wintergreen aroma with a refreshing sensation was perceived and lasted longer than with the use of a similar paste without the menthyl ester.

Example 4

A toothpaste was produced by conventional methods from the following ingredients (in parts by weight):

Menthyl ester of N-acetylglycine	0.40
Aluminum hydroxide	42.50
Aluminum oxide	2.00
Sodium lauryl sulfoacetate	1.00

Glycerin	28.00
Gum tragacanth	0.50
Sodium saccharinate	0.05
Methyl <i>p</i> -toluenehydroxybenzoate	0.10
Flavorings	
Natural anethole	0.25
Synthetic anethole	0.25
Ceylon cinnamon oil	0.10
Clove oil	0.05
Coriander oil	0.2
Glycyrrhiza	0.25
Sweet fennel	0.15
Bitter fennel	0.15
Tarragon	0.05
Lemon oil	0.05
Water	23.95

When this paste was used for brushing the teeth, an anise aroma arose without menthol flavor or any refreshing effect and lasted 40 minutes, while when the same composition was used in which the menthyl ester was replaced by a mole-equivalent amount of Brazilian menthol (0.245) and alcohol (0.155), an anise aroma arose with a predominant mint flavor and a refreshing effect, lasting 25 minutes.

Example 5

A mouthwash was produced by mixing the following ingredients (in parts by weight):

Menthyl ester of N-acetylglycine	0.8
95% Ethanol	25
Glycerin	12
Sodium saccharinate	0.05
Lemon oil	0.4
Polyoxyethylene-(20)-sorbitan monolaurate	7
Water	54.75

Before use, this mouthwash was diluted with the same volume of water.

Claims

1. N-acetylglycine menthyl ester.
2. Process for producing N-acetylglycine menthyl ester according to Claim 1, characterized by the fact that glycine is esterified with menthol and acetylated either before or after esterification.
3. Process for producing the ester according to Claim 1, characterized by the fact that the menthol ester of glycine is acetylated.
4. Process for producing the ester according to Claim 1, characterized by the fact that N-acetylglycine is esterified with menthol.
5. Composition or agent consisting of an ester and an orally acceptable vehicle, characterized by the fact that the ester is the menthyl ester of N-acetylglycine.
6. Composition or agent according to Claim 5, characterized by the fact that it contains from 0.025 to 2 weight percent of the ester.
7. Composition or agent according to Claim 5 or 6, characterized by the fact that the vehicle includes a tooth polishing agent.
8. Composition or agent according to Claim 7, characterized by the fact that it contains 5 to 99.5 weight percent polishing agent.
9. Composition or agent according to Claim 7 or 8, characterized by the fact that the vehicle contains a surface active agent.
10. Composition or agent according to Claim 9, characterized by the fact that it contains from 0.01 to 10 weight percent surface active agent.
11. Composition or agent according to one of Claims 1 through 7, characterized by the fact that the vehicle contains a sweetening agent.
12. Composition or agent according to Claim 11, characterized by the

fact that it contains from 0.01 to 5 weight percent of the sweetening agent.

13. Composition or agent according to Claim 5 or 6, characterized by the fact that the vehicle contains aqueous ethanol.

14. Composition or agent according to one of Claims 5 through 13, characterized by the fact that the vehicle contains an aromatizing substance.